40 CFR Part 799

[OPTS-42008; TSH-FRL-2005-2]

Phenylenediamines; Response to Interagency Testing Committee

AGENCY: Environmental Protection Agency (EPA).

ACTION: Advance notice of proposed rulemaking.

SUMMARY: Section 4(e) of the Toxic Substances Control Act (TSCA) established an Interagency Testing Committee to recommend to the Administrator of the EPA a list of chemical substances and mixtures to be considered for the development of test rules under TSCA section 4(a). On May 28, 1980, the ITC recommended that the class phenylenediamines be considered for testing for their toxic effects on human health and the environment. EPA currently feels that toxicological data for the phenylenediamines and the exposure potential of thirteen PDAs are sufficient to warrant proposing those 13 of the 47 chemicals recommended by the ITC for testing under section 4(a)(1)(A). EPA is considering the desirability of placing 34 additional phenylenediamines whose production is low or unknown or that are not currently in production, under other regulatory authority such as section 5(a) significant new use rule or a section 8(a) reporting rule.

DATE: Written comments should be submitted on or before March 9, 1982.

ADDRESSES: Written comments should be addressed to: Document Control Officer, (TS-793), Office of Pesticides and Toxic Substances, Environmental Protection Agency, Rm. E-401, 401 M St., SW., Washington, D.C. 20460.

Comments should bear the identifying notation OPTS 42008. The administrative record, including comments, is available for public inspection in Rm. E-107 at the address noted above from 8:00 a.m. to 4:00 p.m. Monday through Friday, except legal holidays.

FOR FURTHER INFORMATION CONTACT: Dr. Douglas Bannerman, Acting Director, Industry Assistance Office (TS-799), Office of Toxic Substances, Environmental Protection Agency, 401 M St., SW., Washington, D.C. 20460, Toll free: (800–424–9065). In Washington D.C.: (554–1404). Outside the USA: Operator–202–544–1404).

SUPPLEMENTARY INFORMATION:

I. Introduction

Section 4(a) of TSCA authorizes the Administrator of EPA to promulgate regulations requiring testing of chemical substances and mixtures in order to develop data relevant to determining the risks that such chemicals may present to health and the environment.

In order to make a section 4(a)(1)(A) finding, EPA must determine that the manufacture, distribution in commerce, processing, use or disposal of a chemical substance or mixture, or any combination of such activities, may present an unreasonable risk of injury to health or the environment, that insufficient data exist to characterize the potential effects of that chemical to human health and the environment, and that testing is necessary to develop such data. In order to make a section 4(a)(1)(B) finding, EPA must determine that a substance is produced in substantial quantities and that there is or may be significant or substantial human exposure or substantial environmental release of that substance, that there are insufficient data to characterize the potential effects of that chemical to human health and the environment, and that testing is necessary to develop such data.

Section 4(e) of TSCA established the Interagency Testing Committee (ITC) to recommend chemicals to the Administrator of EPA for priority consideration for test rules under section 4(a). The Committee may at any one time designate up to 50 of its recommendations for priority attention by EPA. Within 12 months of that designation, EPA either must initiate rulemaking to require testing or publish in the Federal Register reasons for not doing so.

The ITC's Sixth Report to the Administrator published in the Federal Register of May 28, 1980 (45 FR 35897), included a recommendation that the phenylenediamines be tested for their effects on human health and the environment.

The phenylenediamines (PDAs) were defined by the ITC as: "all nitrogen-unsubstituted phenylenediamines with zero to two substituents on the ring selected from the same or different members of the group of halo, nitro, hydroxy, hydroxy-lower alkoxy, lower-alkyl and lower-alkoxy. For this purpose, the term 'lower' is defined as a group containing between one and four carbons." The ITC listed 50 PDA's as occurring on the TSCA Public Inventory. EPA's review has identified 47 of these chemicals (listed in Table A) that fall within the stated definitioin. Note that, in the Sixth ITC Report, #18 and #32 are the same chemical and #29 and #38 are the same chemical. Number 22 (CAS 1477550) on the ITC list is a xylene derivative that does not fit the definition. The total number of CAS numbers listed in Table A, which is based upon the original ITC list, is 49, while the total number of chemicals is 47.

There is some ambiguity in the counting of PDA owing to possible equivalency of free bases and their salts. EPA has for the present chosen to use the ITC list as its reference point, retaining various salts of a single PDA as individual entries.

Thus, for example, the 13 compounds listed in Table C represent only nine distinct PDA bases. For purposes of EPA's preliminary determination of exposure potential, the total production of all base and salt forms of a particular PDA was used. Public comments on this ANPR will help the Agency to decide how to treat this kind of redundancy.

Table A—Phenylenediamines, (as adapted from the May 28, 1980 Federal Register List) [1]

CAS No. and Name

(1) 95545 o-Diaminobenzene
(2) 95705 2.5-Diaminotoluene
(3) 95807 1.3-Diamino-4-methylbenzene
(4) 95830 o-Phenylenediamine, 4-chloro-
(5) 99569 o-Phenylenediamine, 4-nitro-
(6) 106503 p-Diaminobenzene
(7) 108452 m-Diaminobenzene
(8) 108714 3.5-Diaminotoluene
(9) 137097 2.4-Diaminophenol dihydrochloride
(10) 496720 1.2-Diamino-4-methylbenzene
(11) 541695 m-Phenylenediammonium dichloride
(12) 541708 m-Phenylenediamine, sulfate (1:1)
(13) 614948 m-Phenylenediamine, 4-methoxy-, dihydrochloride
(14) 615054 m-Phenylenediamine, 4-methoxy-
(15) 616281 1.2-Phenylenediamines dihydrochloride
(16) 615452 1.4-Benzenediamine, 2-methyl-, dihydrochloride
(17) 615463 p-Phenylenediamine, 2-chloro-, dihydrochloride
(18) 615509 2.5-Diaminotoluene sulfate (1:1)
(19) 624180 p-Phenylenediamine dihydrochloride
(20) 823405 2.6-Diamino-1-methylbenzene
(21) 1197371 o-Phenylenediamine, 4-ethoxy-
(22) 2687254 1.2-Diamino-3-methylbenzene
(23) 3663238 o-Phenylenediamine, 4-butyl-
(24) 5042557 m-Phenylenediamine, 5-nitro-
(25) 5131588 m-Phenylenediamine, 4-nitro-
(26) 5131602 m-Phenylenediamine, 4-chloro-
(27) 5307028 p-Diaminoanisole
(28) 5307142 p-Phenylenediamine, 2-nitro-
(29) 6219676 m-Phenylenediamine, 2-nitro-
(30) 6219712 p-Phenylenediamine, 2-nitro-
(31) 6219778 o-Phenylenediamine, 4-nitro-, sulfate
(32) 6369591 1.4-Benzenediamine, 2-methyl-, dihydrochloride
(33) 15872738 4.6-Diamino-o-cresol
(34) 16245776 p-Phenylenediamine sulfate
(35) 13268529 p-Phenylenediamine, 2-nitro-, dihydrochloride
(36) 20103097 p-Phenylenediamine, 2.5-dichloro-
(37) 25376458 Diaminotoluene
(38) 39156417 2.4-Diaminoanisole sulfate
(39) 42389300 1.2-Benzenediamine, 5-chloro-3-nitro-
(40) 62654175 1.4-Benzenediamine, ethanedioate (1:1)
(41) 65879449 4.6-Diamino-2-methylphenol, hydrochloride
(42) 66422955 Ethanol, 2-(2.4-diaminophenoxy)-, dihydrocholoride
(43) 67801063 1.3-Benzenediamine, 4-ethoxy-, dihydrochloride
(44) 68015985 1.3-Benzenediamine, 4-ethoxy-sulfate (1:1)
(45) 68239805 m-Phenylenediamine, 4-chloro-, sulfate
(46) 68239827 1.2-Benzenediamine, 4-nitro, sulfate (1:1)
(47) 68239838 1.4-Benzenediamine, 2-nitro-, sulfate (1:1)
(48) 68459983 1.2-Benzenediamine, 4-chloro-, sulfate (1:1)
(49) 68966847 1.3-Benzenediamine, ar-ethyl-ar-methyl

[1] The list published in the Federal Register has been edited and validated so that only those chemicals adhering to the ITC definition are included. One chemical, number 22, a.a'-Diamino-m-xylene (CAS No. 1477550) has been deleted from the list. Number 22 is deleted because it does not adhere to the ITC's definition of a phenylenediamine given in the Federal Register.

Note also that for CAS No. 6369591 (Federal Register No. 33, No. 32 in Table A) that the correct name is 1.4-Benzenediamine, 2-methyl-, sulfate, not 1.4-Benzenediamine, ethanedioate (1:1) as listed in the Federal Register. Numbers 29 and 38 are the same chemical with two different CAS numbers.

The names of the chemicals are the names listed on the Ninth Collective Index. There may be differences within the test of some of the CAS numbers. The names of the chemicals used in the text are the names for the chemicals which are found in the literature.

The ITC recommended that the untested and inadequately tested compounds should be evaluated through testing for carcinogenicity, mutagenicity, teratogenicity, and for other health effects (with particular emphasis on blood, bone marrow and nervous system disorders), through epidemiological studies on those phenylenediamines for which there is significant human exposure potential, and through assessment of environmental effects, particularly on organisms repeatedly exposed from constant release sources. The ITC felt that the high production levels of some phenylenediamines and the "demonstrated or suspected health effects associated with certain phenylenediamines, and the general usage of these kinds of chemicals" justified the designation of the phenylenediamines for assessment by EPA and consideration of rulemaking under section 4(a).

II. Response of EPA to the ITC Report

A. Analysis by EPA of Data on Phenylenediamines

EPA has reviewed the ITC report, the available data on which the recommendation was based, information obtained from EPA's own information-gathering activities, and materials submitted to the Agency by the public. EPA's search of computerized data banks for data on the phenylenediamines first identified over 100,000 articles as potentially containing information on phenylenediamines; EPA staff were able to reduce this number to 7480 pertinent citations. Additional screening by EPA staff identified approximately 900 of these articles from which an evaluation of the production, use, exposure, and health and environmental hazard of phenylenediamines is being made. A list of these articles is included in the public record of this proceeding. The Agency is also reviewing submissions of data by E. I. duPont De Nemours & Company; The Cosmetic, Toiletry and Fragrance Association; the Natural Resources Defense Council; and the Food and Drug Administration.

Preliminary analyses of exposure, production, use and effects of these substances have been completed; a summary of this information is presented in Unit III below. Several issues have been identified which the Agency will try to resolve through updated literature searching, continued evaluation of literature in hand, and evaluation of public comment on the issues presented in Unit IV of this Notice.

B. Tentative Section 4(a) Findings for Phenylenediamines

This advance notice of proposed rulemaking (ANPR) is EPA's response to the ITC. By publishing this ANPR EPA is initiating rulemaking on the phenylenediamines, as required by TSCA section 4(e). This notice also presents a summary of the Agency's thinking about the phenylenediamines based on its preliminary analyses, certain tentative conclusions, its proposed rulemaking schedule, and the major issues that have been identified during the Agency's evaluation to date of phenylenediamines that must be resolved before issuance of a test rule.

Applying the section 4(a) criteria to a complex structural class such as the PDAs is difficult because of the variations in properties and commercial status among the different compounds.

The Agency believes that either a section 4(a)(1)(A)(i) or a section 4(a)(1)(B)(i) finding could be made for variously chosen sets of PDAs, but has tentatively decided that the best approach to take for this class of chemicals is to make section 4(a)(1)(A) findings, because the data available to the Agency on exposure and release potential are uneven while the toxicological effects and physicochemical properties are better documented and more consistent than the exposure data. On the basis of the known toxicological characteristics (Table B) of certain PDAs, the structural similarities among group members, the numerous possibilities for structural transformation, and the toxicological activities of other aromatic amines to mammals, fish and aquatic invertebrates, testing of the 13 PDAs in Table C for health and environmental effects and environmental fate is tentatively being considered for proposal under section 4(a)(1)(A).

TABLE B.—TOXICITY OF PHENYLENEDIAMINES*

	Carcinogenicity**							Mutagenicity		Chromosome damage	Cell transformation	Teratogenicity	Reproduction	Neurotoxicity	Other
	BL	K	F	L	M	T	S	Bacteria	Eukaryotes						
o-phenylenediamine (95545)[a].				+[c]				+		[b]					
m-phenylenediamine (108452).								+	+		?				
m-phenylenediamine dihydrochloride (541695).	–[a]														+
p-phenylenediamine (106503).								+	+	–					
p-phenylenediamine dihydrochloride (624180)[a].	±	±			±	±									
4-chloro-o-phenylenediamine (95830)[a].	+			±	±	±[c]		+							+
4-chloro-m-phenylenediamine (5131602)[a].				+[e]	±	±									
2-chloro-p-phenylenediamine sulfate (6219712)[a].	±			±[c]	±	±[c]									
2-nitro-p-phenylenediamine (5307142)[a].				+[e]	±			+	+	+[f]	+	+			
4-nitro-m-phenylenediamine (5131588).								+							
4-nitro-o-phenylenediamine (99569)[a].				±[c]	±	±	±	+	+	+[f]	+	+			
2,4-toluenediamine (95807)[a].	±	±		±[e]	+	±		+	+		+				+.
2,5-toluenediamine (95705).								+			+	+[i]			
2,5-toleuenediamine sulfate (6369591)[a].	±	±													
-toluenediamine 323405).								+							
2,6-toluenediamine dihydrochloride (823405)[a].		±		±[c]	±	±[c]									

TABLE B.—TOXICITY OF PHENYLENEDIAMINES*—Continued

	Carcinogenicity**							Mutagenicity		Chromosome damage	Cell transformation	Teratogenicity	Reproduction	Neurotoxicity	Other
	BL	K	F	L	M	T	S	Bacteria	Eukaryotes						
3,4-toluenediamine (496720).								+							
2,5-diminoanisole (5307028).								+			−				
2,4-diaminoanisole (615054).								+	+[g]						
2,4-diaminoanisole sulfate (39156417)[e].		±	±	±[c]	±	+[c]	+								
4-methoxy-m-phenylenediamine (6219676).									+						
4-ethoxy-m-phenylenediamine (68015985).								±							

After: Brennan, et al. 1981 and Sontag 1981.

*Positive response = +; Negative response = −; Low frequency observed or possible dose related response = ±; equivocal response = ?; blank space = response not observed for cancer and not documented for mutagenicity, chromosome damage, and cell transformation, carcinogenicity responses not otherwise noted are for rats.

**Bladder = BL; Kidney = K; Forestomach = F; Liver = L; Mammary gland = M; Thyroid gland = T; Skin and skin glands = S.

[a] 78 week treatment.

[b] 103 week treatment.

[c] Carcinogenicity in mice, too.

[d] Significant only in mice.

[f] Rat micronucleus test = −; Human peripheral blood lymphocyte, Chinese hamster prostrate, and C3H/10T mouse cells = +.

[g] Equivocal response in L5178Y mouse lymonocytes; positive *Drosophila melanogaster*.

[h] Reported as non-carcinogenic, but data not available.

[i] Subcutaneous injection 5, 50 mg/kg, between days 7–14 in mice caused skeletal abnormalities.

[j] Embryotoxic without shown teratogenic activity (Marks 1980).

[k] Medullary and spinal type convulsions within 20–30 min. after injection (Hanzlik 1928).

TABLE C.—EFFECTS FOR WHICH TESTING IS BEING CONSIDERED

CAS No. and chemical name	(1,000 lbs) production and imports	Exposure NIOSH predicted	Oncogenicity	Teratogenicity	Reproductive toxicity	Mutagenicity	Acute toxicity	Chronic toxicity	Epidemiology	Chemical fate	Aquatic toxicity*	Avian toxicity	Plant toxicity	Bioconcentration
(1) 95807 2,4-diaminotoluene.	139,400–233,500			X	X	X	X	X	X	X	X	X	X	X
(2) 823405 2,6-diaminotoluene.	21,000–110,000		X											
(3) 25376458 diaminotoluene, unspecified isomers.	50,000–100,010	7281	X	X	X	X	X	X	X	X	X	X	X	X
(4) 106503 p-phenylenediamine.	36,500–48,000	61537	X	X	X	X		X	X	X	X	X	X	X
(5) 16245775 p-phenylenediamine sulfate.	1–10		X	X	X	X	X	X	X	X	X	X	X	X
(6) 624180 p-phenylenediamine dihydrochloride.	<1		X	X	X	X	X	X	X	X	X	X	X	X
(7) 2687254 2,3-diaminotoluene.	2,000–22,000		X	X	X	X	X	X	X	X	X	X	X	X
(8) 496720 3,4-diaminotoluene.	500–6,000		X	X	X	X	X	X	X	X	X	X	X	X
(9) 108452 m-phenylenediamine.	100–1,136	12590		X	X			X	X	X	X	X	X	X
(10) 541708 m-phenylenediamine sulfate (1:1).	<1		X	X	X	X	X	X	X	X	X	X	X	X
(11) 95705 2,5-diaminotoluene.	100–1,000		X	X	X	X	X	X	X	X	X	X	X	X
(12) 6369591 2,5-diaminotoluene sulfate (unspecified [illegible]).	3–113	8680	X	X	X	X	X	X	X	X	X	X	X	X
[illegible]5545 o-phenylenediamine.	100–200 (1700–1800)		X	X	X	X	X	X	X	X	X	X	X	X

( ) Values estimated by Mathtech (1980).

*Both vertebrate and invertebrate testing are being considered.

These PDAs are those believed to have significant exposure potential and the highest production. The Agency is also considering the possibility of proposing short term testing for health and environmental effects under section 4(a)(1(A) for chemicals that are otherwise tentatively not being considered for testing.

The effects tentatively identified by EPA as needing testing include oncogenicity, mutagenicity (gene mutations and chromosomal aberrations), teratogenicity, neurotoxicity, reproductive effects, and environmental effects including environmental fate.

EPA does not intend to include the remaining phenylenediamines in a section 4(a) test rule because they are produced in low quantities, are known not to have sufficient exposure subject to TSCA jurisdiction (see Unit III below) or are not currently in commercial production.

III. Summary of Technical Background Information

The following analysis is based upon the Agency's preliminary evaluation of the PDAs. EPA's investigation is continuing. Information received in response to this ANPR could markedly change the tentative conclusions set forth below.

A. Human Exposure Potential

Combined reported domestic production for 22 of the phenylenediamines listed by the ITC exceeds 227 million pounds (103,000 kkg) from 32 different manufacturing companies. Eight of the PDAs have been reported as being produced in unspecified amounts and 18 of the PDAs are reported as not commercially available. NIOSH estimates indicate that a combined total of approximately 64,000 people (after correction for non-TSCA exposure) are potentially exposed in the work place to seven phenylenediamines whose total combined production is approximately 50 million pounds (22.7 kkg). The remaining 15 PDAs for which production data are known have a combined production of 177 million pounds (80.5 kkg), or more than three times that of those included in the NIOSH study; in the absence of specific exposure information or estimates it is reasonable to expect that the number of workers exposed to these 15 PDAs may equal or exceed that obtained in the NIOSH study.

Phenylenediamines are used in dyes, either directly as color-yielding compounds or as intermediates, as curing agents, reagents, and chemical intermediates, and in the synthesis of fungicides, drugs and vulcanization accelerators (see table D for a summary of uses) (Mathtech 1980, Sutta et al. 1981a).

TABLE D.—USES OR POTENTIAL USES OF 47 PHENYLENEDIAMINE COMPOUNDS

CAS	Unkown	Synthesize fungicides	Dye intermediate	Hair dye	Dye other than hair	Chemical intermediate	Photographic developing agent	Identification agent	Synthesize drugs	Culing agent	Reagent	Synthesize antioxidants/antiozonants	Fiber production	Vulcanization acceleration
(1) 95-54-5.		X	X	Y				X						
(2) 95-70-5.			X	X										
(3) 95-80-7.				X	X	X								
(4) 95-83-0.			X	X					X	X	X			
(5) 99-56-9.				X				X			X			
(6) 106-50-3.			X	X		X	X				X	X	X	X
(7) 108-45-2.			X	X		X	X			Y			X	
(8) 108-71-4.	X													
(9) 137-09-7.				X	X	X					X			
(10) 496-72-0.				Y		Y						X		
(11) 541-69-5.				Y							X			
(12) 541-70-8.	X													
(13) 614-94-8.				X	X									
(14) 615-05-4.			X	X	X									
(15) 615-28-1.	X													
(16) 615-45-2.	X													
(17) 615-46-3.	X													
(18) 615-50-9.			X	X										
(19) 624-18-0.				Y	X						X			
(20) 823-40-5.			Y			X								
(21) 1197-37-1.				Y										
(22) 2687-25-4.												X		
(23) 3663-23-8.	X													
(24) 5042-55-7				Y										
(25) 5131-58-8.				Y	Y									
(26) 5131-60-2.			X	Y	X									

TABLE D.—USES OR POTENTIAL USES OF 47 PHENYLENEDIAMINE COMPOUNDS—Continued

CAS	Unkown	Synthesize fungicides	Dye intermediate	Hair dye	Dye other than hair	Chemical intermediate	Photographic developing agent	Identification agent	Synthesize drugs	Culing agent	Reagent	Synthesize antioxidants/antiozonants	Fiber production	Vulcanization acceleration
(27) 5307-02-8.				Y										
(28) 5307-14-2.				X	X									
(29) [2]6219-67-6.				X	X									
(30) 6219-71-2.				X	Y								Y	
(31) 6219-77-8.	X													
(32) [1]6369-59-1.														
(33) 15872-73-8.	X													
(34) 16245-77-5.	X													
(35) 18266-52-9.	X													
(36) 20103-09-7.	X													
(37) 25376-45-8.					Y	X				Y				
(38) [2]39156-41-7.				X	X									
(39) 42389-30-0.				Y										
(40) 62654-17-5.	X													
(41) 65879-44-9.	X													
(42) 66422-95-5.	X													
(43) 67801-06-3.	X													
(44) 68015-98-5.				Y	Y									
(45) 68239-80-5.	X													
(46) 68239-82-7.	X													
(47) 68239-83-8.				X	Y									
(48) 68459-98-3.	X													
(49) 68966-84-7.	X													

X—Indicates use for the stated purpose.
Y—Indicates possible use for the stated purpose.
[1] Numbers 18 and 32 are the same chemical with two different CAS numbers.
[2] Numbers 29 and 38 are the same chemical with two different CAS numbers.
(Sutta et al. 1981a)

It is apparent from the uses of PDAs summarized in Table D that TSCA-covered exposure to these substances is most likely to occur in various workplace situations. However, there are a few applications that could cause a large number of consumer exposures, including use in photographic developers to which amateur darkroom workers may be exposed, and use in dyes, to the extent that such dyes are sold for consumer use or may migrate from fabrics in contact with human skin. Furthermore, human exposure to PDAs may also occur indirectly via substances that are made from PDAs and which retain the PDA moiety (or substructure) in a form that may be chemically or biologically regenerated as a PDA. Examples of such substances include toluene diisocyanate, some photographic developers, and materials formed in synthetic fiber production (Sutta et al. 1981c).

In addition, there seems to be interchangeability among PDAs for some uses, and the Agency must take into account the possibility that, if a particular commercial PDA is ordered to be tested, or found to be hazardous, it may be replaced by another PDA, previously of little or no commercial importance, that is poorly characterized toxicologically. For example, dyes containing different PDAs which produce similar colors on hair can be substituted for each other (Sutta, et al. 1981c). Thus, the Agency is aware that 2,4-toluendediamine (2,4-TDA), 4-methoxy-m-phenylenediamine (MMPDA) and 4-ethoxy-m-phenylenediamine (EMPDA) have served as substitutes for each other as hair dye intermediates [1], that all three are mutagenic to bacteria and that 2,4-TDA and MMPDA are carcinogenic to rats (Prival et al. 1980). Sutta, et al (1981c) also report that a product brochure for a 35:65 mixture of 2,3- and 3,4-diaminotoluene lists it as an alternative for o-phenylenediamine.

EPA is aware that p-phenylenediamine, M-phenylenediamine, 2,5-diaminotoluene sulfate, 4-nitro-o-phenylenediamine, 4-methoxy-m-phenylenediamine sulfate, 4-nitro-m-phenylenediamine, 2-chloro-p-phenylenediamine sulfate, m-phenylenediamine dihydrochloride, 4-methoxy-m-phenylenediamine dihydrochloride, 4-ethoxy-m-phenylenediamine sulfate (1:1), p-

[1] Both 2,4-TDA and MMPDA are reported as having been used in dyes other than hair.

diaminoanisole, and 2-nitro-p-phenylenediamine sulfate have substantial uses in the manufacture of hair dye either as active ingredients in permanent hair dyes or as intermediates in the synthesis of semipermanent dyes. Approximately 15 million individuals per year are potentially exposed to these PDAs as a result of either personal use or in the application of hair dyes to other people (Sutta et al., 1980). However, the use of phenylenediamine hair dyes falls under the authority of the Food Drug and Cosmetic Act of 1938. Because section 3 of TSCA excludes cosmetics subject to the Food, Drug and Cosmetic Act from TSCA jurisdiction, exposure potential as a result of hair dye use is not being considered as a basis for testing in this Notice. The TSCA-usage and exposure potential of the first three chemicals listed above appear to be sufficient to justify their inclusion among the PDAs for which EPA is tentatively considering proposing testing. If information is furnished that there is minimal or no TSCA usage of the remaining substances named above, the Agency will reconsider its tentative determination to retain these substances in the broader group of PDAs for the purpose of this rulemaking evaluation.

B. Environmental Release of Phenylenediamines

Data for environmental release of phenylenediamines are sparse. A materials balance analysis for 2,4-diaminotoluene (2,4-DAT) indicates that of the 433 million pounds (196,900 kkg) produced, over 23.3 million lbs (10,600 kkg) of 2,4-DAT was potentially released to the environment during its production and use in 1977 (Johnston et al. 1980). Sutta, *et al.* (1981c) estimated that, during the production of toluene diisocyanate (TDI), less than 4 percent of the total volume of phenylenediamines consumed during TDI production would be released into the environment. From this predicted release, these authors projected the annual PDA release from this activity into environmental compartments to be 11–18 million pounds (4.4–7.2 kkg) to land, 3–4.5 million lbs. (1.2-1.8 kkg) to water, and 120 lbs (48 kg) to the atmosphere.

EPA has found little information on the loss of PDAs to the environment when used as additives: p-phenylenediamine used as an anti-oxidant in rubber for pipejoints in sewer mains did not leach into the water after 7 years (Mulcock, 1976). EPA has no information on whether the other PDAs demonstrate similar immobility when they serve as additives in dyes, plastics, rubber, etc.

C. Environmental Persistence and Fate

Aromatic amines are relatively reactive compounds that may undergo fairly rapid transformation in the environment, for example the oxidation of o- and p-PDAs to quinones. Thus the lifetime of some PDAs could be short under environmental conditions. The compounds m-phenylenediamine, o-phenylenediamine, p-phenylenediamine, and 2,4-diaminotoluene can undergo some biodegradation in both soil and water environments (Pitter 1976, Horitsu et al. 1977, Richardson 1980). In laboratory experiments, activated sludge biodegraded the concentrations of p-, m-, and o-phenylenediamines to 80 percent, 60 percent, and 33 percent, respectively, of their original concentrations within 120 hours (Pitter 1976, Pitter and Radkova 1974, Verschueren 1977). Under actual use conditions, however, even assuming biodegradation rates of this magnitude, PDAs may enter terrestrial and acquatic ecosystems at levels that will result in a net accumulation of substance over time. Furthermore, the PDAs include a broad range of structure types, some of which may be considerably more stable than others, for example because of the presence of deactivating substituents such as nitro groups, or because of the formation of stable complexes with metals (in the case of o-PDAs). Pesticides derived from the aromatic amine 3,4-dichloroaniline undergo soil microbial or chemical transformation to 3,3′, 4,4′-tetrachloroazobenzene, a highly toxic chemical (Bartha 1971, Bartha & Prama 1967, Bartha & Pramer 1968). Similar reactions are theoretically possible with phenylenediamines, but the Agency is unaware of any studies that would clarify the point.

As illustrated in Table E, the octanol/water partition coefficient is low for the eight PDAs for which Log P_{oct} has been determined. Hence, there appears to be little potential for bioaccumulation of these PDAs. However, data have not been identified to substantiate this prediction.

TABLE E.—PHYSICAL PROPERTIES OF PHENYLENEDIAMINES

Name Cas No.	MW	Lg $P_{oct/w}$	MP °C	BP °C
2,5 diaminotoluene 95705.	122.17	0.25	64	273/274.
2,4 diaminotoluene 95807.	122.17	.50	99	292.
3,5 diaminotoluene 108714.	122.17	NA	40	283-285.
3,4 diaminotoluene 496720.	122.17	.65	88.5	265 (subl).
2,6 diaminotoluene 823405.	122.17	.5	105	
2,3 diaminotoluene 2687254.	122.17	.65	63/64	255.

TABLE E.—PHYSICAL PROPERTIES OF PHENYLENEDIAMINES—Continued

Name Cas No.	MW	Lg $P_{oct/w}$	MP °C	BP °C
p-phenylenediamine 106503.	108.15	−.25	145/147	267.
m-phenylenediamine 108452.	108.15	0	61/64	282/284.
o-phenylenediamine 95545.	108.15	.15	102/103	256/258.
(Brennan & Siczek 1981.)				

D. Toxic Effects Potential

The carcinogenic activities of 14 PDAs in mice and rats have been studied (USEPA 1980a). Six PDAs are reported as being carcinogenic (Table B). Of these, o-phenylenediamine, 2,4-diaminoanisole, and 4-chloro-o-phenylenediamine were carcinogenic to both rats and mice. Eight PDAs were not carcinogenic under the reported experimental conditions (NCI 1978c, NCI 1978d, NCI 1979c, USEPA 1980a). Bladder, liver, kidney, thyroid and skin cancer have been noted to occur at low frequencies during shorter term chronic tests of PDAs in rats and mice (Table B). Long term (103+ weeks) chronic studies have shown that bladder tumors may be caused by chemicals which, tested for a shorter period such as 78 weeks, did not provide clear evidence for induction of bladder cancers (Sontag 1981).

The Agency's preliminary study of the reports of the carcinogenicity testing has generated concern that the actual concentrations of phenylenediamine being received by the test animals may have been lower than the concentration of PDA mixed with the feed. In the studies evaluated to date, administration of PDAs has been in the feed. These reports indicate that the mixing of a PDA into the feed resulted in an uneven distribution of PDA within the sample (NCI 1979c, NCI 1979d, NCI 1980). The chemical properties of PDAs are such that PDAs could be partially oxidized in the feed before the experiment was completed. E. I. du Pont de Nemours & Co. (1980) reports that when o-PDA was mixed with animal feed, only 75 percent of the initially mixed concentration could be recovered by extraction after 24 hours and that less than 50 percent could be recovered after 7 days. Only for 2,6-toluenediamine dihydrochloride was the compound concentration reported as being stable for 2 weeks at temperatures up to 45° C (NCI 1980).

Eight PDAs are reported as being mutagenic to bacterial cells and not further tested; six phenylenediamines have been shown to be mutagenic to both bacteria and eukaryotes (Table E). 2,5-Diaminoanisole (CAS 5307028) is reported as being mutagenic to bacteria and not to L5178Y mouse lymphoma cells. 4-Nitor-o-phenylenediamine (CAS 99569) and 2-nitro-p-phenylenediamine (CAS 99569) and 2-nitro-p-phenylenediamine (CAS 5307142) are reported to cause chromosome damage to Chinese hamster prostate cells and to C3H/10T½ mouse cells. 4-Methoxy-m-phenylenediamine sulfate (CAS 6219-676) is reported to be mutagenic to *Drosophila* and to have ambiguous mutagenic effects on mouse lymphoma cells (USEPA 1980a). The preliminary analysis of mutagenicity data indicates that untested PDAs have a potential to cause both gene mutations and chromosomal aberrations.

Teratogenic activity has been identified for three PDAs. Subcutaneous injections of 2,5-diaminotoluene into mice during days 7-14 of gestation resulted in skeletal anomalies, exencephaly and congenital facial cleft (Inouye and Murakami 1977). In a separate experiment subcutaneous injections of 2-nitro-p-phenylenediamine and 4-nitro-o-phenylenediamine were teratogenic to mice. However, 2, 5-diaminotoluene was not teratogenic in this experiment (Marks et al 1980). The Marks et al (1980) experiment does provide evidence of a potential adverse reproductive effect of 2,5-diaminotoluene since embtyotoxicity was noted during this experiment. No teratogenic activity was observed when PDAs were mixed into hair dyes and topically administered to rabbits and rats prior to and during gestation (Wernick et al 1975, Hogan and Rinehart 1977).

A potential for neurotoxic effects of PDAs is indicated by one study in which unspecified doses of injected m-PDA and p-PDA caused convulsions in four mammalian species, with neuromuscular effects in frogs (Hanzlik 1923).

Other toxic effects have been noted during the range-finding determinations for the NCI bioassays, such as slight hematopoietic effects and cytoplasmic vacuolation of hepatocytes and bile duct hyperplasia for 2,4-diaminotoluene and renal medullary hemorrhage for 2,6-toluenediamine dihydrochloride. 2, 4-Diaminoanisole sulfate did not produce noticeable abnormalities in rats and mice during the range finding tests.

2,4-Diaminotoluene induces methemoglobinemia; because this effect is characteristic of many aromatic amines (de Bruin 1978), other PDAs besides 2,4-DAT are suspect for this property.

Although the Agency has little information on the environmental effects of PDAs, other better characterized aromatic amines, such as anilines, are known to be toxic to aquatic invertebrates and vertebrates.

PDAs have the potential to be converted metabolically and nonbiologically to a variety of compounds that may still be toxicologically active in humans or other organisms. Quinones, hydroxylated or acetylated derivatives, and azo or azoxy derivatives (see above, Unit III.C) are possible examples. o-PDAs are potential metal-chelating agents that could disturb physiological systems dependent on metal ions. The Agency has little information on the metabolic fate either of those PDAs that have undergone some toxicological testing or those that have not.

IV. Issues

1. Are the exposure-related data on which EPA is basing its tentative section 4(a)(1)(A) testing decision accurate? In order to help the Agency refine its analysis of the phenylenediamines, EPA solicits the submission of more detailed exposure information on individual PDAs, including the numbers of workers at manufacturing, processing, and use sites actually involved with PDAs, use patterns, and potential exposure of workers, consumers and the general public. The Agency is likewise soliciting information on the release, potential release, disposal, transformation products, persistence and bioaccumulation of individual phenylenediamines. The Agency is particularly interested in receiving occupational and environmental monitoring data for these chemicals or their transformation products. The Agency will reconsider which PDAs should be tested if new production and other exposure-related data on the compounds warrant this.

2. The Agency is considering monitoring the future production of the 34 PDAs listed in Table F, and any other PDAs which might be manufactured and which conform to the ITC definition, under TSCA section 5(a) significant new use rule (SNUR) or under a TSCA section 8(a) reporting rule.

TABLE F.—PHENYLENEDIAMINES FOR WHICH ALTERNATIVE ACTION UNDER TSCA IS BEING EVALUATED

CAS	
1. Phenylenediamines produced but with no production data published	
108714	3,5-diaminotoluene.
1197371	4-ethoxy-o-phenylenediamine.
5042557	5-nitro-m-phenylenediamine.
3663238	4-butyl-o-phenylenediamine.
68966847	1,3-benzenediamine ar-ethyl-ar-methyl.
615281	o-phenylenediamine dihydrochloride.
68239827	4-nitro-o-phenylenediamine sulfate.
5131602	4-chloro-m-phenylenediamine.
2. Phenylenediamines not produced commercially	
615452	2,5-diaminotoluene dihydrochloride.
62654175	p-phenylenediamine ethandioate.
541695	m-phenylenediamine dihydrochloride.
614948	4-methoxy-m-phenylenediamine dihydrochloride.
67801063	4-ethoxy-m-phenylenediamine dihydrochloride.
68015985	4-ethoxy-m-phenylenediamine sulfate (1:1).
5307028	p-diaminoanisole.
18266529	2-nitro-p-phenylenediamine dihydrochloride.
68239638	2-nitro-p-phenylenediamine sulfate.
42389300	5-chloro-3-nitro-o-phenylenediamine.
6219778	4-nitro-o-phenylenediamine dihydrochloride.
68239805	4-chloro-m-phenylenediamine sulfate.
68459988	4-chloro-m-phenylenediamine sulfate.
615463	2-chloro-p-phenylenediamine dihydrochloride.
20103097	2,5-dichloro-p-phenylenediamine.
15872738	4,6-diamino-o-cresol.
65879449	4,6-diamino-o-cresol hydrochloride.
66422955	2-(2,4-diaminophenoxy) ethanol dihydrochloride.
3. Phenylenediamines with production levels reported to be less than 1 million pounds or which are used primarily in hair dyes	
5307142	2-nitro-p-phenylenediamine.
5131588	4-nitro-m-phenylenediamine.
95830	4-chloro-o-phenylenediamine.
6219712	2-chloro-p-phenylenediamine sulfate.
137097	2,4-diaminophenol dihydrochloride.
39156417	4-methoxy-m-phenylenediamine sulfate.
99569	4-nitro-o-phenylenediamine.
615054	4-methoxy-m-phenylenediamine.

The Agency has identified eight PDAs from the ITC listing that have been reported as being produced but for which production data are not published (Table F, Part 1). Eighteen PDAs on the ITC list have been characterized as not commercially available (Table F, Part 2). Eight PDA's have been identified whose current production volume appears to be quite low or whose use and exposure patterns result primarily or exclusively from their use in hair dyes (Table F, Part 3). In light of the large number of PDAs that have shown some form of serious toxicity such as carcinogenicity or mutagenicity, and the possible interchangeability of PDAs, some form of alternative action appears to be the best way to avoid requiring testing of relatively low production and exposure PDAs now but still protect the public against substitution of a poorly characterized, potentially hazardous PDA in the future. The Agency invites comments on the alternatives to testing discussed below.

(A) A significant new use rule (SNUR) under section 5(a) would define certain new uses of PDAs as "significant new uses." A person responsible for manufacturing or processing for a use defined by the rule would be required to submit a notice of intent under section 5(a)(1) at least 90 days before manufacturing or processing for the new use occurs. The information required to be submitted includes identity of the compound and byproducts, projected uses, amounts of substance to be produced and processed for each use, environmental and health data, numbers of persons expected to be exposed and duration of the exposure, and the manner in which the material is to be disposed. The Agency would be responsible for reviewing data on any significant new use to assess its effect on human health and the environment. A SNUR would let EPA take appropriate followup action if a significant increase in exposure is projected. EPA has a period of 90 days in which to review the health and environmental implications of the new use, but may extend the period up to an additional 90 days for good cause.

(B) Placing PDAs on the 5(b)(4) list in combination with issuing a SNUR for these chemicals would provide EPA the information and opportunity for followup action in alternative (A) and also provide additional data that may help EPA assess the potential risks of these chemicals. Section 5(b)(2)(A) requires persons submitting a notice on chemicals subject to a SNUR that are also on the 5(b)(4) list to submit data which they believe show that the manufacturing, processing, distribution in commerce, use and disposal of the chemical substance will not present an unreasonable risk of injury to health or the environment.

(C) A section 8(a) reporting rule would require the same information to be reported as a SNUR in alternative (A). However, there are differences in who is required to report and the frequency of reporting. For example, a section 8(a) rule could require regular periodic reporting or could require persons to report when certain events occurred. Furthermore, it would extend to all manufacturers and processors (except small ones), unlike a SNUR which reaches only persons manufacturing and processing a chemical for a new use. Unlike a SNUR, a section 8(a) rule, on its own, could not require reporting by small manufacturers and processors.

(D) Placing PDAs on the 5(b)(4) list in combination with a section 8(a) reporting requirement would have the same effect as alternative (C) but would also subject small manufacturers and processors to the section 8(a) reporting requirement.

3. Is environmental fate and effects testing of PDAs needed? EPA has encountered little information that sheds light on the environmental fate of PDAs. Because of the known biological activity of PDAs, their release potential and their potential to undergo a variety of transformations that may not be detoxifying, and the known hazards of aromatic amines, such as anilines, to aquatic organisms, the Agency is considering proposing both fate and environmental toxicity testing for all of the chemicals listed in Table C. However, the Agency has tentatively decided that testing for bioaccumulation is not necessary for PDAs whose Log P_{oct} values are known to be lower than 1. Octanol/water partition coefficient determination is being considered as a requirement for the remaining PDAs listed in Table C.

The Agency would welcome the submission of data on environmental fate and persistence of these substances, including monitoring data obtained near known points of release. The Agency is also interested in obtaining information on potentially harmful transformation products and bioaccumulation of individual phenylenediamines, and on additional testing which will adequately characterize the environmental toxicity of PDAs.

4. For a given test organism, should some or all PDAs be administered as salts rather than as free bases? This would be expected to increase the stability of the materials, but changes the possible exposure routes and pharmacokinetic properties (for example, vapor pressures of the salts are lower than those of the free bases, while water solubilities are much greater). Resolution of the compound stability question discussed in Unit III.D will influence decisions on which chemicals should be tested and the most reliable means of administration of the chemical to test organisms. Should all PDAs be administered by the same route? This would increase comparability of results, but might result in some discrepancies between acutal and experimental exposure routes.

5. How many individual phenylenediamines should be tested? The Agency is aware that requiring full testing of the entire class or even the 13 PDAs listed in Table C may be impractical and unecessary.

As mentioned in Unit II.B, phenylenediamines are a complex structural class. Within the class, there do not appear to be any clear structural relationships with respect to PDA oncogenic activity. The 22 PDAs for which at least one toxicological study has been completed to date have all shown some adverse biological activity. It is highly likely that the remaining untested PDAs will also show biological activity when they are tested. The Agency is therefore considering proposing testing for the 13 substances that are reported to be produced in quantities exceeding one million pounds (454 kkg). EPA is soliciting opinions as to both the number of PDAs to be proposed for testing and the specific PDAs that should be proposed for testing (Issues 6 and 7 bear on this question). Should full testing be required of all PDAs selected for testing? Full testing for some and short term tests for others? Should a respresentative sampling be chosen? If so, what basis should be used to select the sample chemicals?

6. Which of the PDAs not characterized for carcinogenicity should be individually tested for their carcinogenic activity? In its Sixth Report published in the Federal Register of May 28, 1980 (45 FR 35897), the ITC argued that, since aromatic (mono-& polycyclic) amines have been shown to be carcinogenic, then the phenylenediamines would" . . . *a priori* . . . (be) suspect as a result of belonging to a chemical class known to have certain properties associated with carcinogenicity." Because most of the oncogenicity tests on PDAs were relatively short-duration tests, and because aromatic amines have been associated with slowly induced bladder tumors, the negative results cited for 8 PDAs (see Unit III.D) should be interpreted with caution. Should the chemicals for which negative results were reported under these conditions be retested?

The Agency is considering proposing oncogenicity testing of all inadequately characterized PDAs listed in Table C (including additional testing of some of those chemicals already tested in less than full term bioassays). Because 4-chloro-o-phenylenediamine, 4-chloro-m-phenylenediamine, 2-nitro-p-phenylenediamine, 2,4-toluenediamine and 4-methoxy-m-phenylenediamine, sulfate are oncogenic under experimental conditions, EPA has tentatively decided not to consider additional oncogenicity testing for these chemicals.

The Agency is interested in receiving comment on the adequacy of the existing experimental data to characterize the oncogenicity of the tested phenylenediamines.

7. Should all phenylenediamines be tested for mutagenicity in bacteria or does the large number of positive bacterial mutagenicity tests (see Unit III.D) indicate that only tests in higher organisms need to be conducted?

In general, EPA believes that a positive bacterial mutagenicity test should be followed by testing in

Drosophila. The results of the Drosophila testing would then be used to determine whether additional *in vivo* or *in vitro* mutagenicity would be recommended. Of the compounds in Table E, only 2,6-diaminotoluene and 2,3-diaminotoluene have not undergone bacterial mutagenicity testing and would ordinarily be under tentative consideration for such testing. However, because 14 PDAs are reported positive in bacterial tests, the Agency is considering whether all PDAs should be presumed to have mutagenic potential for the purpose of determining how many PDAs should be subjected to the next stage of mutagenicity testing. The Agency welcomes comments on this issue.

8. Should all of the uncharacterized PDAs selected for testing be tested for teratogenic, reproductive, neurological and other chronic effects? Data on the toxic effects, other than mutagenicity and oncogenicity, are sparse. The data analysed to date for 2,5-diaminotoluene, 2-nitro-p-phenylenediamine, 4-nitro-o-phenylenediamine, m-phenylenediamine, p-phenylenediamine, 2,4-diaminotoluene, and 2,6-toluenediamine dihydrochloride tentatively suggest that teratogenic, reproductive, neurotoxic and other adverse effects may be demonstrated by other members of the class. The Agency welcomes comments on these potential effects of concern.

V. Development of Rulemaking

EPA, after analysis of the comments to the ITC Report and preliminary review of available data, believes that there is reason to proceed with detailed consideration of the recommendations for testing under the rulemaking process identified in TSCA section 4(b).

The purpose of the rule to be proposed is to obtain data which may be evaluated to determine the effect of the chemicals on health and the environment. These data once submitted will be assessed to determine whether sufficient risk is presented to pursue regulatory control. EPA in publishing this ANPR wishes to receive early comment on its tentative basis for requiring testing and on the tests the Agency believes necessary to characterize the effects of the phenylenediamines. The Agency plans to publish a Notice of Proposed Rulemaking by October, 1982.

The Agency will analyze all comments received in response to this ANPR on toxicological effects, exposure, production and use information and other issues. The Agency will also accept any voluntary testing plans submitted for review and comment. These testing plans need not be final for inclusion in the ANPR comments, but should be formal protocols for proper review.

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